

**SYSTEM AND METHOD FOR MEASURING CROSS-SECTIONAL AREAS AND  
PRESSURE GRADIENTS IN LUMINAL ORGANS**

This U.S. Utility Patent Application claims priority to U.S. Provisional Patent Application Serial No. 60/449,266, filed February 21, 2003, and to U.S. Provisional Patent Application Serial No. 60/493,145, filed August 7, 2003, and to U.S. Provisional Patent Application Serial No. 60/502,139, filed September 11, 2003, the contents of each of which are hereby incorporated by reference in their entirety into this disclosure.

Background of the InventionField of the Invention

The present invention relates generally to medical diagnostics and treatment equipment. In particular, the preferred embodiments of the invention relate to methods and apparatus for measuring luminal cross-sectional area of blood vessels, heart valves and other hollow visceral organs.

Background of the Invention*Coronary Heart Disease*

Coronary heart disease is caused by atherosclerotic narrowing of the coronary arteries. It is likely to produce angina pectoris, heart attack or both. Coronary heart disease caused 466,101 deaths in USA in 1997 and is the single leading cause of death in America today. Approximately, 12 million people alive today have a history of heart attack, angina pectoris or both. The break down for males and females is 49% and 51%, respectively. This year, an estimated 1.1 million Americans will have a new or recurrent coronary attack, and more than 40% of the people experiencing these attacks will die as a result. About 225,000 people a year die of coronary attack without being hospitalized. These are sudden deaths caused by cardiac arrest, usually resulting from ventricular fibrillation. More than 400,000 Americans and 800,000 patients world-wide undergo a non-surgical coronary artery interventional procedure each year. Although only introduced in the 1990s, in some laboratories intra-coronary stents are used in 90% of these patients.

Stents increase minimal coronary lumen diameter to a greater degree than percutaneous transluminal coronary angioplasty (PTCA) alone according to the results of two randomized trials using the Palmaz-Schatz stent. These trials compared two initial treatment strategies: stenting alone and PTCA with “stent backup” if needed. In the STRESS trial, there was a significant difference in successful angiographic outcome in favor of stenting (96.1% vs. 89.6%).

#### *Intravascular Ultrasound*

Currently intravascular ultrasound is the method of choice to determine the true diameter of the diseased vessel in order to size the stent correctly. The term “vessel,” as used herein, refers generally to any hollow, tubular, or luminal organ. The tomographic orientation of ultrasound enables visualization of the full 360° circumference of the vessel wall and permits direct measurements of lumen dimensions, including minimal and maximal diameter and cross-sectional area. Information from ultrasound is combined with that obtained by angiography. Because of the latticed characteristics of stents, radiographic contrast material can surround the stent, producing an angiographic appearance of a large lumen, even when the stent struts are not in full contact with the vessel wall. A large observational ultrasound study after angio-graphically guided stent deployment revealed an average residual plaque area of 51% in a comparison of minimal stent diameter with reference segment diameter, and incomplete wall apposition was frequently observed. In this cohort, additional balloon inflations resulted in a final average residual plaque area of 34%, even though the final angiographic percent stenosis was negative (20.7%). These investigators used ultrasound to guide deployment.

However, using intravascular ultrasound as mentioned above requires a first step of advancement of an ultrasound catheter and then withdrawal of the ultrasound catheter before coronary angioplasty thereby adding additional time to the stent procedure. Furthermore, it requires an ultrasound machine. This adds significant cost and time and more risk to the procedure.

#### *Aortic Stenosis*

Aortic Stenosis (AS) is one of the major reasons for valve replacements in adult. AS occurs when the aortic valve orifice narrows secondary to valve degeneration. The aortic valve area is reduced to one fourth of its normal size before it shows a hemodynamic effect.

Because the area of the normal adult valve orifice is typically 3.0 to 4.0 cm<sup>2</sup>, an area 0.75-1.0 cm<sup>2</sup> is usually not considered severe AS. When stenosis is severe and cardiac output is normal, the mean trans-valvular pressure gradient is generally > 50 mmHg. Some patients with severe AS remain asymptomatic, whereas others with only moderate stenosis develop symptoms. Therapeutic decisions, particularly those related to corrective surgery, are based largely on the presence or absence of symptoms.

The natural history of AS in the adult consists of a prolonged latent period in which morbidity and mortality are very low. The rate of progression of the stenotic lesion has been estimated in a variety of hemodynamic studies performed largely in patients with moderate AS. Cardiac catheterization and Doppler echocardiographic studies indicate that some patients exhibit a decrease in valve area of 0.1-0.3 cm<sup>2</sup> per year; the average rate of change is 0.12 cm<sup>2</sup> per year. The systolic pressure gradient across the valve may increase by as much as 10 to 15 mmHg per year. However, more than half of the reported patients showed little or no progression over a 3-9 year period. Although it appears that progression of AS can be more rapid in patients with degenerative calcific disease than in those with congenital or rheumatic disease, it is not possible to predict the rate of progression in an individual patient.

Eventually, symptoms of angina, syncope, or heart failure develop after a long latent period, and the outlook changes dramatically. After onset of symptoms, average survival is < 2-3 years. Thus, the development of symptoms identifies a critical point in the natural history of AS.

Many asymptomatic patients with severe AS develop symptoms within a few years and require surgery. The incidence of angina, dyspnea, or syncope in asymptomatic patients with Doppler outflow velocities of 4 m/s has been reported to be as high as 38% after 2 years and 79% after 3 years. Therefore, patients with severe AS require careful monitoring for development of symptoms and progressive disease.

#### *Indications for Cardiac Catheterization*

In patients with AS, the indications for cardiac catheterization and angiography are to assess the coronary circulation (to confirm the absence of coronary artery disease) and to confirm or clarify the clinical diagnosis of AS severity. If echocardiographic data are typical of severe isolated AS, coronary angiography may be all that is needed before aortic valve replacement (AVR). Complete left- and right-heart catheterization may be necessary to

assess the hemodynamic severity of AS if there is a discrepancy between clinical and echocardiographic data or evidence of associated valvular or congenital disease or pulmonary hypertension.

The pressure gradient across a stenotic valve is related to the valve orifice area and transvalvular flow through Bernoulli's principle. Thus, in the presence of depressed cardiac output, relatively low pressure gradients are frequently obtained in patients with severe AS. On the other hand, during exercise or other high-flow states, systolic gradients can be measured in minimally stenotic valves. For these reasons, complete assessment of AS requires (1) measurement of transvalvular flow, (2) determination of the transvalvular pressure gradient, and (3) calculation of the effective valve area. Careful attention to detail with accurate measurements of pressure and flow is important, especially in patients with low cardiac output or a low transvalvular pressure gradient.

#### *Problems with Current Aortic Valve Area Measurements*

Patients with severe AS and low cardiac output are often present with only modest transvalvular pressure gradients (i.e., < 30 mmHg). Such patients can be difficult to distinguish from those with low cardiac output and only mild to moderate AS. In both situations, the low-flow state and low pressure gradient contribute to a calculated effective valve area that can meet criteria for severe AS. The standard valve area formula (simplified Hakki formula which is  $\text{valve area} = \text{cardiac output} / [\text{pressure gradient}]^{1/2}$ ) is less accurate and is known to underestimate the valve area in low-flow states; under such conditions, it should be interpreted with caution. Although valve resistance is less sensitive to flow than valve area, resistance calculations have not been proved to be substantially better than valve area calculations.

In patients with low gradient stenosis and what appears to be moderate to severe AS, it may be useful to determine the transvalvular pressure gradient and calculate valve area and resistance during a baseline state and again during exercise or pharmacological (i.e., dobutamine infusion) stress. Patients who do not have true, anatomically severe stenosis exhibit an increase in the valve area during an increase in cardiac output. In patients with severe AS, these changes may result in a calculated valve area that is higher than the baseline calculation but that remains in the severe range, whereas in patients without severe AS, the

calculated valve area will fall outside the severe range with administration of dobutamine and indicate that severe AS is not present.

There are many other limitations in estimating aortic valve area in patients with aortic stenosis using echocardiography and cardiac catheterization.. Accurate measurement of the aortic valve area in patients with aortic stenosis can be difficult in the setting of low cardiac output or concomitant aortic or mitral regurgitations. Concomitant aortic regurgitation or low cardiac output can overestimate the severity of aortic stenosis. Furthermore, because of the dependence of aortic valve area calculation on cardiac output, any under or overestimation of cardiac output will cause inaccurate measurement of valve area. This is particularly important in patients with tricuspid regurgitation. Falsely measured aortic valve area could cause inappropriate aortic valve surgery in patients who do not need it.

#### *Other visceral organs*

Visceral organs such as the gastrointestinal tract and the urinary tract serve to transport luminal contents (fluids) from one end of the organ to the other end or to an absorption site. The esophagus, for example, transports swallowed material from the pharynx to the stomach. Diseases may affect the transport function of the organs by changing the luminal cross-sectional area, the peristalsis generated by muscle, or by changing the tissue components. For example, strictures in the esophagus and urethra constitute a narrowing of the organ where fibrosis of the wall may occur. Strictures and narrowing can be treated with distension, much like the treatment of plaques in the coronary arteries.

#### Summary of the Invention

The present invention provides for a system for measuring cross-sectional areas and pressure gradients in luminal organs. The present invention also comprises a method and apparatus for measuring cross-sectional areas and pressure gradients in luminal organs, such as, for example, blood vessels, heart valves, and other visceral hollow organs.

In one embodiment, the system comprises an impedance catheter capable of being introduced into a treatment site, a solution delivery source for injecting a solution through the catheter into the treatment site, a constant current source enabling the supply of constant electrical current to the treatment site, and a data acquisition system enabling the measurement of parallel conductance at the treatment site, whereby enabling calculation of cross-sectional area at the treatment site.

In one embodiment, the catheter further comprises an inflatable balloon along its longitudinal axis.

In one embodiment, the catheter further comprises a pressure transducer near the distal end of the catheter.

In one approach, a method of measuring the cross-sectional area of a targeted treatment site comprises: introducing an impedance catheter into a treatment site; providing constant electrical current to the treatment site; injecting a first solution of first compound; measuring a first conductance value at the treatment site; injecting a second solution of a second compound; measuring a second conductance value at the treatment site; calculating the cross-sectional area of the treatment site based on the first and second conductance values and the conductivities of the first and second compounds.

In one approach, a method of constructing a three-dimensional model of a treatment site that comprises: introducing an impedance catheter into a treatment site; measuring a first cross-sectional area at a first point; adjusting the position of the catheter; measuring a second cross-sectional area at a second point, and so on; constructing a three-dimensional model of the treatment site along the longitudinal axis based on multiple longitudinal cross-sectional area measurements.

#### Brief Description of the Drawings

Figure 1A illustrates a balloon catheter having impedance measuring electrodes supported in front of the stenting balloon;

Figure 1B illustrates a balloon catheter having impedance measuring electrodes within and in front of the balloon;

Figure 1C illustrates a catheter having an ultrasound transducer within and in front of balloon;

Figure 1D illustrates a catheter without a stenting balloon;

Figure 1E illustrates a guide catheter with wire and impedance electrodes;

Figure 1F illustrates a catheter with multiple detection electrodes;

Figure 2A illustrates a catheter in cross-section proximal to the location of the sensors showing the leads embedded in the material of the probe;

Figure 2B illustrates a catheter in cross-section proximal to the location of the sensors showing the leads run in separate lumens;

Figure 3 is a schematic of one embodiment of the system showing a catheter carrying impedance measuring electrodes connected to the data acquisition equipment and excitation unit for the cross-sectional area measurement;

Figures 4A show the detected filtered voltage drop as measured in the blood stream before and after injection of 1.5% NaCl solution;

Figure 4B shows the peak-to-peak envelope of the detected voltage shown in Figure 4A;

Figures 5A show the detected filtered voltage drop as measured in the blood stream before and after injection of 0.5% NaCl solution;

Figure 5B shows the peak-to-peak envelope of the detected voltage shown in Figure 5A;

Figure 6 illustrates balloon distension of the lumen of the coronary artery;

Figure 7 illustrates balloon distension of a stent into the lumen of the coronary artery;

Figure 8A illustrates the voltage recorded by a conductance catheter with a radius of 0.55 mm for various size vessels (vessel radii of 3.1, 2.7, 2.3, 1.9, 1.5 and 0.55 mm for the six curves, respectively) when a 0.5% NaCl bolus is injected into the treatment site; and

Figure 8B illustrates the voltage recorded by a conductance catheter with a radius of 0.55 mm for various size vessels (vessel radii of 3.1, 2.7, 2.3, 1.9, 1.5 and 0.55 mm for the six curves, respectively) when a 1.5% NaCl bolus is injected into the treatment site.

#### Detailed Description of the Preferred Embodiments

This invention makes accurate measures of the luminal cross-sectional area of organ stenosis within acceptable limits to enable accurate and scientific stent sizing and placement in order to improve clinical outcomes by avoiding under or over deployment and under or over sizing of a stent which can cause acute closure or in-stent re-stenosis. In one embodiment, an angioplasty or stent balloon includes impedance electrodes supported by the catheter in front of the balloon. These electrodes enable the immediate measurement of the cross-sectional area of the vessel during the balloon advancement. This provides a direct measurement of non-stenosed area and allows the selection of the appropriate stent size. In one approach, error due to the loss of current in the wall of the organ and surrounding tissue is corrected by injection of two solutions of NaCl or other solutions with known

conductivities. In another embodiment impedance electrodes are located in the center of the balloon in order to deploy the stent to the desired cross-sectional area. These embodiments and procedures substantially improve the accuracy of stenting and the outcome and reduce the cost.

Other embodiments make diagnosis of valve stenosis more accurate and more scientific by providing a direct accurate measurement of cross-sectional area of the valve annulus, independent of the flow conditions through the valve. Other embodiments improve evaluation of cross-sectional area and flow in organs like the gastrointestinal tract and the urinary tract

Embodiments of this invention overcome the problems associated with determination of the size (cross-sectional area) of luminal organs, such as, for example, in the coronary arteries, carotid, femoral, renal and iliac arteries, aorta, gastrointestinal tract, urethra and ureter. Embodiments also provide methods for registration of acute changes in wall conductance, such as, for example, due to edema or acute damage to the tissue, and for detection of muscle spasms/contractions.

As described below, in one preferred embodiment, there is provided an angioplasty catheter with impedance electrodes near the distal end 19 of the catheter (i.e., in front of the balloon) for immediate measurement of the cross-sectional area of a vessel lumen during balloon advancement. This catheter includes electrodes for accurate detection of organ luminal cross-sectional area and ports for pressure gradient measurements. Hence, it is not necessary to change catheters such as with the current use of intravascular ultrasound. In one preferred embodiment, the catheter provides direct measurement of the non-stenosed area, thereby allowing the selection of an appropriately sized stent. In another embodiment, additional impedance electrodes may be incorporated in the center of the balloon on the catheter in order to deploy the stent to the desired cross-sectional area. The procedures described herein substantially improve the accuracy of stenting and improve the cost and outcome as well.

In another embodiment, the impedance electrodes are embedded within a catheter to measure the valve area directly and independent of cardiac output or pressure drop and therefore minimize errors in the measurement of valve area. Hence, measurements of area are direct and not based on calculations with underlying assumptions. In another

embodiment, pressure sensors can be mounted proximal and distal to the impedance electrodes to provide simultaneous pressure gradient recording.

## CATHETER

We designed and build the impedance or conductance catheters illustrated in Figures 1A-1F. With reference to the exemplary embodiment shown in Figure 1A, four wires were threaded through one of the 2 lumens of a 4 Fr catheter. Here, electrodes 26 and 28, are spaced 1 mm apart and form the inner (detection) electrodes. Electrodes 25 and 27 are spaced 4-5 mm from either side of the inner electrodes and form the outer (excitation) electrodes.

In one approach, dimensions of a catheter to be used for any given application depend on the optimization of the potential field using finite element analysis described below. For small organs or in pediatric patients the diameter of the catheter may be as small as 0.3 mm. In large organs the diameter may be significantly larger depending on the results of the optimization based on finite element analysis. The balloon size will typically be sized according to the preferred dimension of the organ after the distension. The balloon may be made of materials, such as, for example, polyethylene, latex, polyesterurethane, or combinations thereof. The thickness of the balloon will typically be on the order of a few microns. The catheter will typically be made of PVC or polyethylene, though other materials may equally well be used. The excitation and detection electrodes typically surround the catheter as ring electrodes but they may also be point electrodes or have other suitable configurations. These electrodes may be made of any conductive material, preferably of platinum iridium or a carbon-coated surface to avoid fibrin deposits. In the preferred embodiment, the detection electrodes are spaced with 0.5-1 mm between them and with a distance between 4-7 mm to the excitation electrodes on small catheters. The dimensions of the catheter selected for a treatment depend on the size of the vessel and are preferably determined in part on the results of finite element analysis, described below. On large catheters, for use in larger vessels and other visceral hollow organs, the electrode distances may be larger.

Referring to Figures 1A, 1B, 1C and 1D, several embodiments of the catheters are illustrated. The catheters shown contain to a varying degree different electrodes, number and

optional balloon(s). With reference to the embodiment shown in Figure 1A, there is shown an impedance catheter 20 with 4 electrodes 25, 26, 27 and 28 placed close to the tip 19 of the catheter. Proximal to these electrodes is an angiography or stenting balloon 30 capable of being used for treating stenosis. Electrodes 25 and 27 are excitation electrodes, while electrodes 26 and 28 are detection electrodes, which allow measurement of cross-sectional area during advancement of the catheter, as described in further detail below. The portion of the catheter 20 within balloon 30 includes an infusion port 35 and a pressure port 36.

The catheter 20 may also advantageously include several miniature pressure transducers (not shown) carried by the catheter or pressure ports for determining the pressure gradient proximal at the site where the cross-sectional area is measured. The pressure is preferably measured inside the balloon and proximal, distal to and at the location of the cross-sectional area measurement, and locations proximal and distal thereto, thereby enabling the measurement of pressure recordings at the site of stenosis and also the measurement of pressure-difference along or near the stenosis. In one embodiment, shown in Figure 1A, Catheter 20 advantageously includes pressure port 90 and pressure port 91 proximal to or at the site of the cross-sectional measurement for evaluation of pressure gradients. As described below with reference to Figures 2A, 2B and 3, in one embodiment, the pressure ports are connected by respective conduits in the catheter 20 to pressure sensors in the data acquisition system 100. Such pressure sensors are well known in the art and include, for example, fiber-optic systems, miniature strain gauges, and perfused low-compliance manometry.

In one embodiment, a fluid-filled silastic pressure-monitoring catheter is connected to a pressure transducer. Luminal pressure can be monitored by a low compliance external pressure transducer coupled to the infusion channel of the catheter. Pressure transducer calibration was carried out by applying 0 and 100 mmHg of pressure by means of a hydrostatic column.

In one embodiment, shown in Figure 1B, the catheter 39 includes another set of excitation electrodes 40, 41 and detection electrodes 42, 43 located inside the angioplastic or stenting balloon 30 for accurate determination of the balloon cross-sectional area during angioplasty or stent deployment. These electrodes are in addition to electrodes 25, 26, 27 and 28.

In one embodiment, the cross-sectional area may be measured using a two-electrode system. In another embodiment, illustrated in Figure 1F, several cross-sectional areas can be measured using an array of 5 or more electrodes. Here, the excitation electrodes 51, 52, are used to generate the current while detection electrodes 53, 54, 55, 56 and 57 are used to detect the current at their respective sites.

The tip of the catheter can be straight, curved or with an angle to facilitate insertion into the coronary arteries or other lumens, such as, for example, the biliary tract. The distance between the balloon and the electrodes is usually small, in the 0.5-2 cm range but can be closer or further away, depending on the particular application or treatment involved.

In another embodiment, shown in Figure 1C the catheter 21 has one or more imaging or recording device, such as, for example, ultrasound transducers 50 for cross-sectional area and wall thickness measurements. As shown in this embodiment, the transducers 50 are located near the distal tip 19 of the catheter 21.

Figure 1D illustrates an embodiment of the impedance catheter 22 without an angioplastic or stenting balloon. This catheter also possesses an infusion or injection port 35 located proximal relative to the excitation electrode 25 and pressure port 36.

With reference to the embodiment shown in Figure 1E, the electrodes 25, 26, 27, 28 can also be built onto a wire 18, such as, for example, a pressure wire, and inserted through a guide catheter 23 where the infusion of bolus can be made through the lumen of the guide catheter 37.

With reference to the embodiments shown in Figures 1A, 1B, 1C, 1D, 1E and 1F, the impedance catheter advantageously includes optional ports 35, 36, 37 for suction of contents of the organ or infusion of fluid. The suction/infusion port 35, 36, 37 can be placed as shown with the balloon or elsewhere both proximal or distal to the balloon on the catheter. The fluid inside the balloon can be any biologically compatible conducting fluid. The fluid to inject through the infusion port or ports can be any biologically compatible fluid but the conductivity of the fluid is selected to be different from that of blood (e.g., NaCl).

In another embodiment (not illustrated), the catheter contains an extra channel for insertion of a guide wire to stiffen the flexible catheter during the insertion or data recording. In yet another embodiment (not illustrated), the catheter includes a sensor for measurement of the flow of fluid in the body organ.

## SYSTEM FOR DETERMINING CROSS-SECTIONAL AREA AND PRESSURE GRADIENT

*The operation of the impedance catheter 20 is as follows:* With reference to the embodiment shown in Figure 1A for electrodes 25, 26, 27, 28, conductance of current flow through the organ lumen and organ wall and surrounding tissue is parallel; i.e.,

$$G(z,t) = \frac{CSA(z,t) \cdot C_b}{L} + G_p(z,t) \quad [1a]$$

where  $G_p(z,t)$  is the effective conductance of the structure outside the bodily fluid (organ wall and surrounding tissue), and  $C_b$  is the specific electrical conductivity of the bodily fluid which for blood generally depends on the temperature, hematocrit and orientation and deformation of blood cells and  $L$  is the distance between the detection electrodes. Equation 1 can be rearranged to solve for cross sectional area  $CSA(t)$ , with a correction factor,  $\alpha$ , if the electric field is non-homogeneous, as

$$CSA(z,t) = \frac{L}{\alpha C_b} [G(z,t) - G_p(z,t)] \quad [1b]$$

where  $\alpha$  would be equal to 1 if the field were completely homogeneous. The parallel conductance,  $G_p$ , is an offset error that results from current leakage.  $G_p$  would equal 0 if all of the current were confined to the blood and hence would correspond to the cylindrical model given by Equation [10]. In one approach, finite element analysis is used to properly design the spacing between detection and excitation electrodes relative to the dimensions of the vessel to provide a nearly homogenous field such that  $\alpha$  can be considered equal to 1. Our simulations show that a homogenous or substantially homogenous field is provided by (1) the placement of detection electrodes substantially equidistant from the excitation electrodes and (2) maintaining the distance between the detection and excitation electrodes substantially comparable to the vessel diameter. In one approach, a homogeneous field is achieved by taking steps (1) and/or (2) described above so that  $\alpha$  is equals 1 in the foregoing analysis.

At any given position,  $z$ , along the long axis of organ and at any given time,  $t$ , in the cardiac cycle,  $G_p$  is a constant. Hence, two injections of different concentrations and/or conductivities of NaCl solution give rise to two equations:

$$C_1 \bullet CSA(z,t) + L \bullet G_p(z,t) = L \bullet G_1(z,t) \quad [2]$$

and

$$C_2 \bullet CSA(z,t) + L \bullet G_p(z,t) = L \bullet G_2(z,t) \quad [3]$$

which can be solved simultaneously for CSA and  $G_p$  as

$$CSA(z,t) = L \frac{[G_2(z,t) - G_1(z,t)]}{[C_2 - C_1]} \quad [4]$$

and

$$G_p(z,t) = \frac{[C_2 \bullet G_1(z,t) - C_1 \bullet G_2(z,t)]}{[C_2 - C_1]} \quad [5]$$

where subscript “1” and subscript “2” designate any two injections of different NaCl concentrations and/or conductivities. For each injection  $k$ ,  $C_k$  gives rise to  $G_k$  which is measured as the ratio of the root mean square of the current divided by the root mean square of the voltage. The  $C_k$  is typically determined through in vitro calibration for the various NaCl concentrations and/or conductivities. The concentration of NaCl used is typically on the order of 0.45 to 1.8%. The volume of NaCl solution is typically about 5 ml, but sufficient to displace the entire local vascular blood volume momentarily. The values of  $CSA(t)$  and  $G_p(t)$  can be determined at end-diastole or end-systole (i.e., the minimum and maximum values) or the mean thereof.

Once the CSA and  $G_p$  of the vessel are determined according to the above embodiment, rearrangement of equation [1] allows the calculation of the specific electrical conductivity of blood in the presence of blood blow as

$$C_b = \frac{L}{CSA(z,t)} [G(z,t) - G_p(z,t)] \quad [6]$$

In this way, equation [1b] can be used to calculate the CSA continuously (temporal variation as for example through the cardiac cycle) in the presence of blood.

In one approach, a pull or push through is used to reconstruct the vessel along its length. During a long injection (e.g., 10-15 s), the catheter can be pulled back or pushed forward at constant velocity  $U$ . Equation [1b] can be expressed as

$$CSA(U \bullet t, t) = \frac{L}{C_b} [G(U \bullet t, t) - G_p(U \bullet t, t)] \quad [7]$$

where the axial position,  $z$ , is the product of catheter velocity,  $U$ , and time,  $t$ ; i.e.,  $z = U \bullet t$ .

For the two injections, denoted by subscript “1” and subscript “2”, respectively, we can consider different time points  $T_1$ ,  $T_2$ , etc. such that equation [7] can be written as

$$CSA_1(U \bullet T_1, t) = \frac{L}{C_1} [G_1(U \bullet T_1, t) - G_{p1}(U \bullet T_1, t)] \quad [8a]$$

$$CSA_1(U \bullet T_1, t) = \frac{L}{C_2} [G_2(U \bullet T_1, t) - G_{p1}(U \bullet T_1, t)] \quad [8b]$$

and

$$CSA_2(U \bullet T_2, t) = \frac{L}{C_1} [G_1(U \bullet T_2, t) - G_{p2}(U \bullet T_2, t)] \quad [9a]$$

$$CSA_2(U \bullet T_2, t) = \frac{L}{C_2} [G_2(U \bullet T_2, t) - G_{p2}(U \bullet T_2, t)] \quad [9b]$$

and so on. Each set of equations [8a], [8b] and [9a], [9b], etc. can be solved for  $CSA_1$ ,  $G_{p1}$  and  $CSA_2$ ,  $G_{p2}$ , respectively. Hence, we can measure the CSA at various time intervals and hence of different positions along the vessel to reconstruct the length of the vessel. In one embodiment, the data on the CSA and parallel conductance as a function of longitudinal position along the vessel can be exported from an electronic spreadsheet, such as, for example, an Excel file, to AutoCAD where the software uses the coordinates to render a 3-Dimensional vessel on the monitor.

For example, in one exemplary approach, the pull back reconstruction was made during a long injection where the catheter was pulled back at constant rate by hand. The catheter was marked along its length such that the pull back was made at 2 mm/sec. Hence, during a 10 second injection, the catheter was pulled back about 2 cm. The data was continuously measured and analyzed at every two second interval; i.e., at every 4 mm. Hence, six different measurements of CSA and  $G_p$  were made which were used to reconstruction the CSA and  $G_p$  along the length of the 2 cm segment.

*Operation of the impedance catheter 39:* With reference to the embodiment shown in Figure 1B, the voltage difference between the detection electrodes 42 and 43 depends on the magnitude of the current (I) multiplied by the distance (D) between the detection electrodes and divided by the conductivity (C) of the fluid and the cross-sectional area (CSA) of the artery or other organs into which the catheter is introduced. Since the current (I), the distance (L) and the conductivity (C) normally can be regarded as calibration constants, an inverse

relationship exists between the voltage difference and the CSA as shown by the following equations:

$$\Delta V = \frac{I \cdot L}{C \cdot CSA} \quad [10a]$$

or

$$CSA = \frac{G \cdot L}{C} \quad [10b]$$

where G is conductance expressed as the ratio of current to voltage ( $I/\Delta V$ ). Equation [10] is identical to equation [1b] if we neglect the parallel conductance through the vessel wall and surrounding tissue because the balloon material acts as an insulator. This is the cylindrical model on which the conductance method is used.

As described below with reference to Figures 2A, 2B, 3, 4 and 5, the excitation and detection electrodes are electrically connected to electrically conductive leads in the catheter for connecting the electrodes to the data acquisition system 100.

Figures 2A and 2B illustrate two embodiments 20A and 20B of the catheter in cross-section. Each embodiment has a lumen 60 for inflating and deflating the balloon and a lumen 61 for suction and infusion. The sizes of these lumens can vary in size. The impedance electrode electrical leads 70A are embedded in the material of the catheter in the embodiment in Figure 2A, whereas the electrode electrical leads 70B are tunneled through a lumen 71 formed within the body of catheter 70B in Figure 2B.

Pressure conduits for perfusion manometry connect the pressure ports 90, 91 to transducers included in the data acquisition system 100. As shown in Figure 2A pressure conduits 95A may be formed in 20A. In another embodiment, shown in Figure 2B, pressure conduits 95B constitute individual conduits within a tunnel 96 formed in catheter 20B. In the embodiment described above where miniature pressure transducers are carried by the catheter, electrical conductors will be substituted for these pressure conduits.

With reference to Figure 3, in one embodiment, the catheter 20 connects to a data acquisition system 100, to a manual or automatic system 105 for distension of the balloon and to a system 106 for infusion of fluid or suction of blood. The fluid will be heated to 37-39° or equivalent to body temperature with heating unit 107. The impedance planimetry system typically includes a constant current unit, amplifiers and signal conditioners. The

pressure system typically includes amplifiers and signal conditioners. The system can optionally contain signal conditioning equipment for recording of fluid flow in the organ.

In one preferred embodiment, the system is pre-calibrated and the probe is available in a package. Here, the package also preferably contains sterile syringes with the fluids to be injected. The syringes are attached to the machine and after heating of the fluid by the machine and placement of the probe in the organ of interest, the user presses a button that initiates the injection with subsequent computation of the desired parameters. The CSA and parallel conductance and other relevant measures such as distensibility, tension, etc. will typically appear on the display panel in the PC module 160. Here, the user can then remove the stenosis by distension or by placement of a stent.

If more than one CSA is measured, the system can contain a multiplexer unit or a switch between CSA channels. In one embodiment, each CSA measurement will be through separate amplifier units. The same may account for the pressure channels.

In one embodiment, the impedance and pressure data are analog signals which are converted by analog-to-digital converters 150 and transmitted to a computer 160 for on-line display, on-line analysis and storage. In another embodiment, all data handling is done on an entirely analog basis. The analysis advantageously includes software programs for reducing the error due to conductance of current in the organ wall and surrounding tissue and for displaying the 2D or 3D-geometry of the CSA distribution along the length of the vessel along with the pressure gradient. In one embodiment of the software, a finite element approach or a finite difference approach is used to derive the CSA of the organ stenosis taking parameters such as conductivities of the fluid in the organ and of the organ wall and surrounding tissue into consideration. In another embodiment, simpler circuits are used; e.g., based on making two or more injections of different NaCl solutions to vary the resistivity of fluid in the vessel and solving the two simultaneous equations [2] and [3] for the CSA and parallel conductance (equations [4] and [5], respectively). In another embodiment, the software contains the code for reducing the error in luminal CSA measurement by analyzing signals during interventions such as infusion of a fluid into the organ or by changing the amplitude or frequency of the current from the constant current amplifier. The software chosen for a particular application, preferably allows computation of the CSA with only a small error instantly or within acceptable time during the medical procedure.

In one approach, the wall thickness is determined from the parallel conductance for those organs that are surrounded by air or non-conducting tissue. In such cases, the parallel conductance is equal to

$$G_p = \frac{CSA_w \bullet C_w}{L} \quad [11a]$$

where  $CSA_w$  is the wall area of the organ and  $C_w$  is the electrical conductivity through the wall. This equation can be solved for the wall  $CSA_w$  as

$$CSA_w = \frac{G_p \bullet L}{C_w} \quad [11b]$$

For a cylindrical organ, the wall thickness,  $h$ , can be expressed as

$$h = \frac{CSA_w}{\pi D} \quad [12]$$

where  $D$  is the diameter of the vessel which can be determined from the circular  $CSA$  ( $D=[4CSA/\pi]^{1/2}$ ).

When the  $CSA$ , pressure, wall thickness, and flow data are determined according to the embodiments outlined above, it is possible to compute the compliance (e.g.,  $\Delta CSA/\Delta P$ ), tension (e.g.,  $P.r$ , where  $P$  and  $r$  are the intraluminal pressure and radius of a cylindrical organ), stress (e.g.,  $P.r/h$  where  $h$  is the wall thickness of the cylindrical organ), strain (e.g.,  $(C-C_d)/C_d$  where  $C$  is the inner circumference and  $C_d$  is the circumference in diastole) and wall shear stress (e.g.,  $4\mu Q/r^3$  where  $\mu$ ,  $Q$  and  $r$  are the fluid viscosity, flow rate and radius of the cylindrical organ for a fully developed flow). These quantities can be used in assessing the mechanical characteristics of the system in health and disease.

## METHOD

In one approach, luminal cross-sectional area is measured by introducing a catheter from an exteriorly accessible opening (e.g., mouth, nose or anus for GI applications; or e.g., mouth or nose for airway applications) into the hollow system or targeted luminal organ. For cardiovascular applications, the catheter can be inserted into the organs in various ways; e.g., similar to conventional angioplasty. In one embodiment, an 18 gauge needle is inserted into the femoral artery followed by an introducer. A guide wire is then inserted into the introducer and advanced into the lumen of the femoral artery. A 4 or 5 Fr conductance

catheter is then inserted into the femoral artery via wire and the wire is subsequently retracted. The catheter tip containing the conductance electrodes can then be advanced to the region of interest by use of x-ray (i.e., fluoroscopy). In another approach, this methodology is used on small to medium size vessels (e.g., femoral, coronary, carotid, iliac arteries, etc.).

In one approach, a minimum of two injections (with different concentrations and/or conductivities of NaCl) are required to solve for the two unknowns, CSA and  $G_p$ . In another approach, three injections will yield three set of values for CSA and  $G_p$  (although not necessarily linearly independent), while four injections would yield six set of values. In one approach, at least two solutions (e.g., 0.5% and 1.5% NaCl solutions) are injected in the targeted luminal organ or vessel. Our studies indicate that an infusion rate of approximately 1 ml/s for a five second interval is sufficient to displace the blood volume and results in a local pressure increase of less than 10 mmHg in the coronary artery. This pressure change depends on the injection rate which should be comparable to the organ flow rate.

In one preferred approach, involving the application of Equations [4] and [5], the vessel is under identical or very similar conditions during the two injections. Hence, variables, such as, for example, the infusion rate, bolus temperature, etc., are similar for the two injections. Typically, a short time interval is to be allowed (1-2 minute period) between the two injections to permit the vessel to return to homeostatic state. This can be determined from the baseline conductance as shown in Figure 4 or 5. The parallel conductance is preferably the same or very similar during the two injections. In one approach, dextran, albumin or another large molecular weight molecule can be added to the NaCl solutions to maintain the colloid osmotic pressure of the solution to reduce or prevent fluid or ion exchange through the vessel wall.

In one approach, the NaCl solution is heated to body temperature prior to injection since the conductivity of current is temperature dependent. In another approach, the injected bolus is at room temperature, but a temperature correction is made since the conductivity is related to temperature in a linear fashion.

In one approach, a sheath is inserted either through the femoral or carotid artery in the direction of flow. To access the lower anterior descending (LAD) artery, the sheath is inserted through the ascending aorta. For the carotid artery, where the diameter is typically on the order of 5-5.5 mm, a catheter having a diameter of 1.9 mm can be used, as determined

from finite element analysis, discussed further below. For the femoral and coronary arteries, where the diameter is typically in the range from 3.5-4 mm, so a catheter of about 0.8 mm diameter would be appropriate. The catheter can be inserted into the femoral, carotid or LAD artery through a sheath appropriate for the particular treatment. Measurements for all three vessels can be made similarly.

Described here are the protocol and results for one exemplary approach that is generally applicable to most arterial vessels. The conductance catheter was inserted through the sheath for a particular vessel of interest. A baseline reading of voltage was continuously recorded. Two containers containing 0.5% and 1.5% NaCl were placed in temperature bath and maintained at 37°. A 5-10 ml injection of 1.5% NaCl was made over a 5 second interval. The detection voltage was continuously recorded over a 10 second interval during the 5 second injection. Several minutes later, a similar volume of 1.5% NaCl solution was injected at a similar rate. The data was again recorded. Matlab was used to analyze the data including filtering with high pass and with low cut off frequency (1200 Hz). The data was displayed using Matlab and the mean of the voltage signal during the passage of each respective solution was recorded. The corresponding currents were also measured to yield the conductance ( $G=I/V$ ). The conductivity of each solution was calibrated with six different tubes of known CSA at body temperature. A model using equation [10] was fitted to the data to calculate conductivity  $C$ . The analysis was carried out in SPSS using the non-linear regression fit. Given  $C$  and  $G$  for each of the two injections, an excel sheet file was formatted to calculate the CSA and  $G_p$  as per equations [4] and [5], respectively. These measurements were repeated several times to determine the reproducibility of the technique. The reproducibility of the data was within 5%. Ultrasound (US) was used to measure the diameter of the vessel simultaneous with our conductance measurements. The detection electrodes were visualized with US and the diameter measurements was made at the center of the detection electrodes. The maximum differences between the conductance and US measurements were within 10%.

Figures 4A, 4B, 5A and 5B illustrate voltage measurements in the blood stream in the left carotid artery. Here, the data acquisition had a the sampling frequency of 75 KHz, with two channels - the current injected and the detected voltage, respectively. The current injected has a frequency of 5 KH, so the voltage detected, modulated in amplitude by the

impedance changing through the bolus injection will have a spectrum in the vicinity of 5 KHz.

With reference to Figure 4A there is shown a signal processed with a high pass filter with low cut off frequency (1200 Hz). The top and bottom portions 200, 202 show the peak-to-peak envelope detected voltage which is displayed in Figure 4B (bottom). The initial 7 seconds correspond to the baseline; i.e., electrodes in the blood stream. The next 7 seconds correspond to an injection of hyper-osmotic NaCl solution (1.5% NaCl). It can be seen that the voltage is decreased implying increase conductance (since the injected current is constant). Once the NaCl solution is washed out, the baseline is recovered as can be seen in the last portion of the Figures 4A and 4B. Figures 5A and 5B shows similar data corresponding to 0.5% NaCl solutions.

The voltage signals are ideal since the difference between the baseline and the injected solution is apparent and systematic. Furthermore, the pulsation of vessel diameter can be seen in the 0.5% and 1.5% NaCl injections (Figures 4 and 5, respectively). This allows determination of the variation of CSA throughout the cardiac cycle as outline above.

The NaCl solution can be injected by hand or by using a mechanical injector to momentarily displace the entire volume of blood or bodily fluid in the vessel segment of interest. The pressure generated by the injection will not only displace the blood in the antegrade direction (in the direction of blood flow) but also in the retrograde direction (momentarily push the blood backwards). In other visceral organs which may be normally collapsed, the NaCl solution will not displace blood as in the vessels but will merely open the organs and create a flow of the fluid. In one approach, after injection of a first solution into the treatment or measurement site, sensors monitor and confirm baseline of conductance prior to injection of a second solution into the treatment site.

The injections described above are preferably repeated at least once to reduce errors associated with the administration of the injections, such as, for example, where the injection does not completely displace the blood or where there is significant mixing with blood. It will be understood that any bifurcation(s) (with branching angle near 90 degrees) near the targeted luminal organ can cause an overestimation of the calculated CSA. Hence, generally the catheter should be slightly retracted or advanced and the measurement repeated. An additional application with multiple detection electrodes or a pull back or push forward

during injection will accomplish the same goal. Here, an array of detection electrodes can be used to minimize or eliminate errors that would result from bifurcations or branching in the measurement or treatment site.

In one approach, error due to the eccentric position of the electrode or other imaging device can be reduced by inflation of a balloon on the catheter. The inflation of balloon during measurement will place the electrodes or other imaging device in the center of the vessel away from the wall. In the case of impedance electrodes, the inflation of balloon can be synchronized with the injection of bolus where the balloon inflation would immediately precede the bolus injection. Our results, however, show that the error due to catheter eccentricity is small.

The CSA predicted by Equation [4] corresponds to the area of the vessel or organ external to the catheter (i.e., CSA of vessel minus CSA of catheter). If the conductivity of the NaCl solutions is determined by calibration from Equation [10] with various tubes of known CSA, then the calibration accounts for the dimension of the catheter and the calculated CSA corresponds to that of the total vessel lumen as desired. In one embodiment, the calibration of the CSA measurement system will be performed at 37°C by applying 100 mmHg in a solid polyphenolenoxide block with holes of known CSA ranging from 7.065 mm<sup>2</sup> (3 mm in diameter) to 1017 mm<sup>2</sup> (36 in mm). If the conductivity of the solutions is obtained from a conductivity meter independent of the catheter, however, then the CSA of the catheter is generally added to the CSA computed from Equation [4] to give the desired total CSA of the vessel.

The signals are generally non-stationary, nonlinear and stochastic. To deal with non-stationary stochastic functions, one can use a number of methods, such as the Spectrogram, the Wavelet's analysis, the Wigner-Ville distribution, the Evolutionary Spectrum, Modal analysis, or preferably the intrinsic model function (IMF) method. The mean or peak-to-peak values can be systematically determined by the aforementioned signal analysis and used in Equation [4] to compute the CSA.

Referring to the embodiment shown in Figure 6, the angioplasty balloon 30 is shown distended within the coronary artery 150 for the treatment of stenosis. As described above with reference to Figure 1B, a set of excitation electrodes 40, 41 and detection electrodes 42,

43 are located within the angioplasty balloon 30. In another embodiment, shown in Figure 7, the angioplasty balloon 30 is used to distend the stent 160 within blood vessel 150.

For valve area determination, it is not generally feasible to displace the entire volume of the heart. Hence, the conductivity of blood is changed by injection of hypertonic NaCl solution into the pulmonary artery which will transiently change the conductivity of blood. If the measured total conductance is plotted versus blood conductivity on a graph, the extrapolated conductance at zero conductivity corresponds to the parallel conductance. In order to ensure that the two inner electrodes are positioned in the plane of the valve annulus (2-3 mm), in one preferred embodiment, the two pressure sensors 36 are advantageously placed immediately proximal and distal to the detection electrodes (1-2 mm above and below, respectively) or several sets of detection electrodes (see, e.g., Figures 1D and 1F). The pressure readings will then indicate the position of the detection electrode relative to the desired site of measurement (aortic valve: aortic-ventricular pressure; mitral valve: left ventricular-atrial pressure; tricuspid valve: right atrial-ventricular pressure; pulmonary valve: right ventricular-pulmonary pressure). The parallel conductance at the site of annulus is generally expected to be small since the annulus consists primarily of collagen which has low electrical conductivity. In another application, a pull back or push forward through the heart chamber will show different conductance due to the change in geometry and parallel conductance. This can be established for normal patients which can then be used to diagnose valvular stenosis.

In one approach, for the esophagus or the urethra, the procedures can conveniently be done by swallowing fluids of known conductances into the esophagus and infusion of fluids of known conductances into the urinary bladder followed by voiding the volume. In another approach, fluids can be swallowed or urine voided followed by measurement of the fluid conductances from samples of the fluid. The latter method can be applied to the ureter where a catheter can be advanced up into the ureter and fluids can either be injected from a proximal port on the probe (will also be applicable in the intestines) or urine production can be increased and samples taken distal in the ureter during passage of the bolus or from the urinary bladder.

In one approach, concomitant with measuring the cross-sectional area and or pressure gradient at the treatment or measurement site, a mechanical stimulus is introduced by way of

inflating the balloon or by releasing a stent from the catheter, thereby facilitating flow through the stenosed part of the organ. In another approach, concomitant with measuring the cross-sectional area and or pressure gradient at the treatment site, one or more pharmaceutical substances for diagnosis or treatment of stenosis is injected into the treatment site. For example, in one approach, the injected substance can be smooth muscle agonist or antagonist. In yet another approach, concomitant with measuring the cross-sectional area and or pressure gradient at the treatment site, an inflating fluid is released into the treatment site for release of any stenosis or materials causing stenosis in the organ or treatment site.

Again, it will be noted that the methods, systems, and catheters described herein can be applied to any body lumen or treatment site. For example, the methods, systems, and catheters described herein can be applied to any one of the following exemplary bodily hollow systems: the cardiovascular system including the heart; the digestive system; the respiratory system; the reproductive system; and the urogenital tract.

*Finite Element Analysis:* In one preferred approach, finite element analysis (FEA) is used to verify the validity of Equations [4] and [5]. There are two major considerations for the model definition: geometry and electrical properties. The general equation governing the electric scalar potential distribution,  $V$ , is given by Poisson's equation as:

$$\nabla \cdot (C \nabla V) = -I \quad [13]$$

where  $C$ ,  $I$  and  $\nabla$  are the conductivity, the driving current density and the del operator, respectively. Femlab or any standard finite element packages can be used to compute the nodal voltages using equation [13]. Once  $V$  has been determined, the electric field can be obtained from as  $E = -\nabla V$ .

The FEA allows the determination of the nature of the field and its alteration in response to different electrode distances, distances between driving electrodes, wall thicknesses and wall conductivities. The percentage of total current in the lumen of the vessel (%I) can be used as an index of both leakage and field homogeneity. Hence, the various geometric and electrical material properties can be varied to obtain the optimum design; i.e., minimize the non-homogeneity of the field. Furthermore, we simulated the experimental procedure by injection of the two solutions of NaCl to verify the accuracy of equation [4]. Finally, we assessed the effect of presence of electrodes and catheter in the lumen of vessel. The error terms representing the changes in measured conductance due to

the attraction of the field to the electrodes and the repulsion of the field from the resistive catheter body were quantified.

We solved the Poisson's equation for the potential field which takes into account the magnitude of the applied current, the location of the current driving and detection electrodes, and the conductivities and geometrical shapes in the model including the vessel wall and surrounding tissue. This analysis suggest that the following conditions are optimal for the cylindrical model: (1) the placement of detection electrodes equidistant from the excitation electrodes; (2) the distance between the current driving electrodes should be much greater than the distance between the voltage sensing electrodes; and (3) the distance between the detection and excitation electrodes is comparable to the vessel diameter or the diameter of the vessel is small relative to the distance between the driving electrodes. If these conditions are satisfied, the equipotential contours more closely resemble straight lines perpendicular to the axis of the catheter and the voltage drop measured at the wall will be nearly identical to that at the center. Since the curvature of the equipotential contours is inversely related to the homogeneity of the electric field, it is possible to optimize the design to minimize the curvature of the field lines. Consequently, in one preferred approach, one or more of conditions (1)-(3) described above are met to increase the accuracy of the cylindrical model.

Theoretically, it is impossible to ensure a completely homogeneous field given the current leakage through the vessel wall into the surrounding tissue. We found that the isopotential line is not constant as we move out radially along the vessel as stipulated by the cylindrical model. In one embodiment, we consider a catheter with a radius of 0.55 mm whose detected voltage is shown in Figures 8A and 8B for two different NaCl solutions (0.5% and 1.5%, respectively). The origin corresponds to the center of the catheter. The first vertical line 220 represents the inner part of the electrode which is wrapped around the catheter and the second vertical line 221 is the outer part of the electrode in contact with the solution (diameter of electrode is approximately 0.25 mm). The six different curves, top to bottom, correspond to six different vessels with radii of 3.1, 2.7, 2.3, 1.9, 1.5 and 0.55 mm, respectively. It can be seen that a "hill" occurs at the detection electrode 220, 221 followed by a fairly uniform plateau in the vessel lumen followed by an exponential decay into the surrounding tissue. Since the potential difference is measured at the detection electrode 220, 221, our simulation generates the "hill" whose value corresponds to the equivalent potential

in the vessel as used in Eq. [4]. Hence, for each catheter size, we varied the dimension of the vessel such that equation [4] is exactly satisfied. Consequently, we obtained the optimum catheter size for a given vessel diameter such that the distributive model satisfies the lumped equations (Equation [4] and [5]). In this way, we can generate a relationship between vessel diameter and catheter diameter such that the error in the CSA measurement is less than 5%. In one embodiment, different diameter catheters are prepackaged and labeled for optimal use in certain size vessel. For example, for vessel dimension in the range of 4-5 mm, 5-7 mm or 7-10 mm, our analysis shows that the optimum diameter catheters will be in the range of 0.9-1.4, 1.4-2 or 2-4.6 mm, respectively. The clinician can select the appropriate diameter catheter based on the estimated vessel diameter of interest. This decision will be made prior to the procedure and will serve to minimize the error in the determination of lumen CSA.

The foregoing description is that of a preferred construction having certain features, aspects, and advantages in accordance with the present invention. Various changes and modifications may be made to the above-described arrangements without departing from the spirit and scope of the invention, as defined by the appended embodiments.